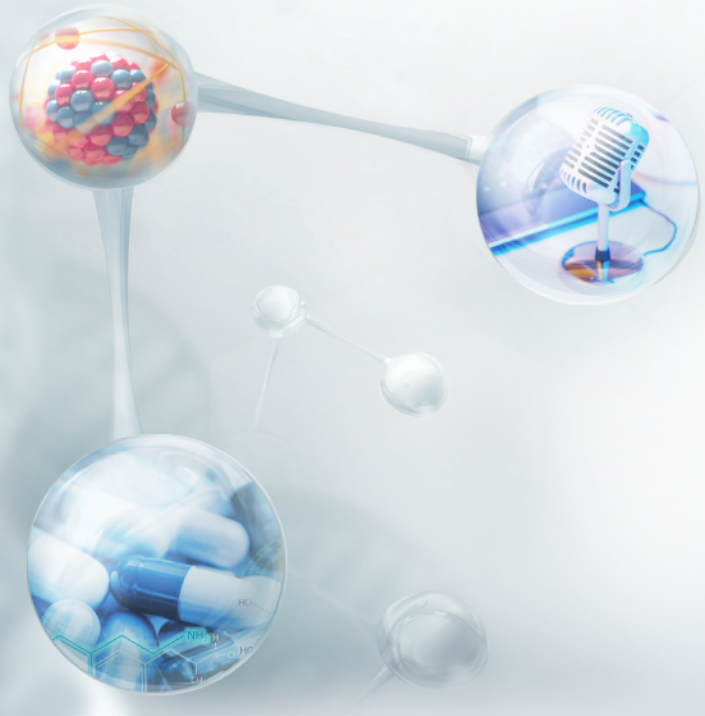
智汇科研 直播间

ThermoFisher SCIENTIFIC



智汇科研宝典

纳米药物

The world leader in serving science

纳米药物学作为纳米生物医学领域的重要分支之一，是研究药物创新、药物再造和药物治疗的新兴学科，在各种重大疾病的诊断和治疗中已显示出重要的作用。

“赛默飞智汇科研直播间”是赛默飞创设的一个学术交流高端平台，每期设置不同科研领域的热点应用主题，邀请该领域领军讲者，分享最新研究成果以及专业技术应用，致力于打造互动对话与学习交流的共享平台，激发启迪科研思路，发掘创新潜能，促进专业领域的长足发展。

纳米药物
论文精华摘要

Contents

A Cooperative Copper Metal–Organic Framework-Hydrogel System Improves Wound Healing in Diabetes

Jisheng Xiao, Siyu Chen, Ji Yi, Hao F. Zhang, and Guillermo A. Ameer*

Biomedical Engineering Department Northwestern University
Chemistry of Life Processes Institute Northwestern University
Department of Surgery Feinberg School of Medicine
Simpson Querrey Institute for BioNanotechnology Northwestern University

ABSTRACT

Chronic nonhealing wounds remain a major clinical challenge that would benefit from the development of advanced, regenerative dressings that promote wound closure within a clinically relevant time frame. The use of copper ions has shown promise in wound healing applications, possibly by promoting angiogenesis. However, reported treatments that use copper ions require multiple applications of copper salts or oxides to the wound bed, exposing the patient to potentially toxic levels of copper ions and resulting in variable outcomes. Herein the authors set out to assess whether copper metal organic framework nanoparticles (HKUST-1 NPs) embedded within an antioxidant thermoresponsive citrate-based hydrogel would decrease copper ion toxicity and accelerate wound healing in diabetic mice. HKUST-1 and poly-(polyethyleneglycol citrate-co-N-isopropylacrylamide) (PPCN) are synthesized and characterized. HKUST-1 NP stability in a protein solution with and without embedding them in PPCN hydrogel is determined. Copper ion release, cytotoxicity, apoptosis, and in vitro migration processes are measured. Wound closure rates and wound blood perfusion are assessed in vivo using the splinted excisional dermal wound diabetic mouse model. HKUST-1 NPs disintegrated in protein solution while HKUST-1 NPs embedded in PPCN (H-HKUST-1) are protected from degradation and copper ions are slowly released. Cytotoxicity and apoptosis due to copper ion release are significantly reduced while dermal cell migration in vitro and wound closure rates in vivo are significantly enhanced. In vivo, H-HKUST-1 induced angiogenesis, collagen deposition, and reepithelialization during wound healing in diabetic mice. These results suggest that a cooperatively stabilized, copper ion-releasing H-HKUST-1 hydrogel is a promising innovative dressing for the treatment of chronic wounds.

Key words: Hydorgel, Metal-organic frameworks, PPCN, Chronic wound healing, HKUST-1

Article link: https://doi.org/10.1002/adfm.201604872

Copper Metal–Organic Framework Nanoparticles Stabilized with Folic Acid Improve Wound Healing in Diabetes

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Department of Chemistry, Northwestern University
Department of Surgery, Feinberg School of Medicine, Northwestern University
Chemistry of Life Processes Institute, Northwestern University
Simpson Querrey Institute for BioNanotechnology, Northwestern University
International Institute for Nanotechnology, Northwestern University

ABSTRACT

The successful treatment of chronic nonhealing wounds requires strategies that promote angiogenesis, collagen deposition, and re-epithelialization of the wound. Copper ions have been reported to stimulate angiogenesis; however, several applications of copper salts or oxides to the wound bed are required, leading to variable outcomes and raising toxicity concerns. We hypothesized that copper-based metal–organic framework nanoparticles (Cu-MOF NPs), referred to as HKUST-1, which are rapidly degraded in protein solutions, can be modified to slowly release Cu^{2+}, resulting in reduced toxicity and improved wound healing rates. Folic acid was added during HKUST-1 synthesis to generate folic-acid-modified HKUST-1 (F-HKUST-1). The effect of folic acid incorporation on NP stability, size, hydrophobicity, surface area, and copper ion release profile was measured. In addition, cytotoxicity and in vitro cell migration processes due to F-HKUST-1 and HKUST-1 were evaluated. Wound closure rates were assessed using the splinted excisional dermal wound model in diabetic mice. The incorporation of folic acid into HKUST-1 enabled the slow release of copper ions, which reduced cytotoxicity and enhanced cell migration in vitro. In vivo, F-HKUST-1 induced angiogenesis, promoted collagen deposition and reepithelialization, and increased wound closure rates. These results demonstrate that folic acid incorporation into HKUST-1 NPs is a simple, safe, and promising approach to control Cu^{2+} release, thus enabling the direct application of Cu-MOF NPs to wounds.

Key words: metal–organic framework, copper, folic acid, wound healing, diabetic ulcer

Article link: https://doi.org/10.1021/acsnano.7b01850

Macrophages as an active tumor-targeting carrier of SN38-nanoparticles for cancer therapy

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[b]*Key Laboratory of Biomass Chemical Engineering of Ministry of Education and Center for Bionanoengineering, College of Chemical and Biological Engineering, Zhejiang University.*
[c]*Department of Respiratory Medicine, The Affiliated Hospital of Hangzhou Normal University.*
[d]*Collaborative Innovation Center of Yangtze River Delta Region Green Pharmaceuticals, Zhejiang University of Technology.*

ABSTRACT

Taking advantage of their enhanced permeability and retention (EPR) effect, nanomedicines have been extensively studied for targeted drug delivery to tumor tissues. However, tumor heterogeneity restricts the EPR effect and drug penetration into tumors, and nanoformulations only generate a limited therapeutic improvement in clinical settings. Macrophages have the inherent ability of tumor homing, stealth in blood circulation, and phagocytosis of particles. In this study, we used peritoneal macrophages as carriers for delivery of SN38 nanoparticles (SN38-NPs) for cancer treatment. SN38-NPs were internalized by macrophages without any obvious effect on viability and migration, and not only induced apoptosis of tumor cells in vitro, but also accumulated in tumor tissues in vivo. In addition, the macrophage-based delivery system for SN38-NPs showed improved therapeutic effect than an equivalent dose of CPT-11 in an A549 subcutaneous tumor model.

Key words: Cell-based drug delivery; Nanoparticle; SN38; Macrophage; Cancer

Article link: https://doi.org/10.1080/1061186X.2017.1419359

The Blood Clearance Kinetics and Pathway of Polymeric Micelles in Cancer Drug Delivery

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Center for Bionanoengineering and Key Laboratory of Biomass Chemical Engineering of Ministry of Education, College of Chemical and Biological Engineering, Zhejiang University
Collaborative Innovation Center of Yangtze River Delta Region Green Pharmaceuticals and [§]College of Chemical Engineering, Zhejiang University of Technology

ABSTRACT

Polymer micelles are one of the most investigated nanocarriers for drug delivery; many have entered clinical trials and some are in clinic use, but their delivery systems have not yet shown the expected high therapeutic efficacy in clinics. Further understanding their in vivo behaviors, particularly how quickly and by what mechanism polymer micelles are cleared (i.e., via micelles or unimers) once injected, is key to solving this dilemma. Herein, we hope to answer these questions for the clinically relevant polyethylene glycol-block-poly(ε-caprolactone) (PEG-PCL) and PEG-block-poly (D,L-lactide) (PEG-PDLLA) micelles. A small fraction of the hydrophobic chain ends was conjugated with a pair of fluorescence resonance energy transfer (FRET) dyes, Cy5 and Cy5.5, and used to fabricate FRET micelles whose FRET efficiency was correlated to the percentage of polymer chains in the micelles, the micelle degree. In vitro, serum proteins induced PEG-PCL micelle dissociation to some extent; mouse serum or blood surprisingly did not induce micelle dissociation but once with shear applied by a microfluidic channel caused most PEG- PCL micelles dissociated. After intravenous administration in mice, the PEG-PCL or PEG-PDLLA micelles were quickly sequestered into the liver as unimers, and the micelle degree in the blood quickly decreased to about 20%. The FRET-imaging experiments showed that in blood vessels the micelles quickly dissociated into unimers, which were found associated with albumin in blood and in liver. Thus, it is concluded that, upon intravenous injection, the shear and the bloodborne proteins (particularly albumin) induced the most (80%) PEG-PCL and PEG-PDLLA micelles to quickly dissociate into unimers, which were sequestered by Kupffer cells, while intact micelles were difficult to clear. These micelles were able to penetrate tumors and were very stable with cell membranes, but dissociated gradually inside cells. These findings on in vivo micelle fate and the clearance mechanism are directional for the rational design of polymer micelles for improved therapeutics; particularly, improving micelle stability in blood is the prerequisite for surface functionalizations such as introducing targeting ligands.

Key words: fluorescence resonance energy transfer, cancer drug delivery, polymeric micelle, micelle disassembly, micelle stability, micelle clearance pathway

Article link: https://doi.org/10.1021/acsnano.8b02830

赛默飞纳米药物研究流程应对方案

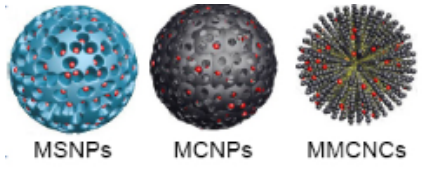
纳米药物

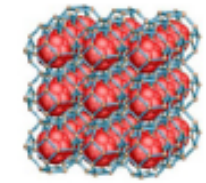
纳米药物类型

纳米药物载体（纳米药物递送系统）

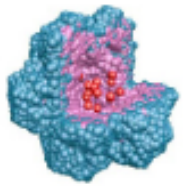
惰性材料作载体

无机多孔材料





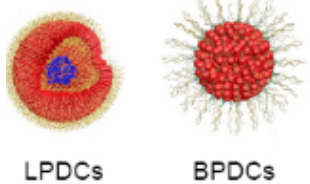
金属有机骨架化合物



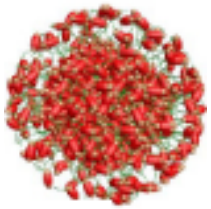
蛋白纳米颗粒

药物是载体的一部分

高分子药物结合物

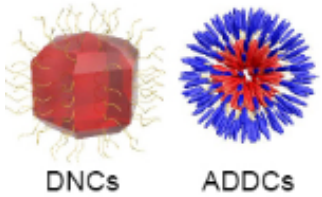


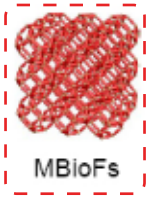
ICP-I型纳米药



纳米粒药物

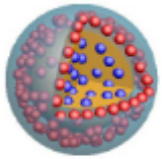
无载体的纳米药物



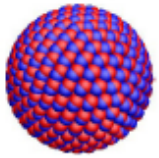


金属-生物分子框架配合物

遵循其他策略的纳米药物



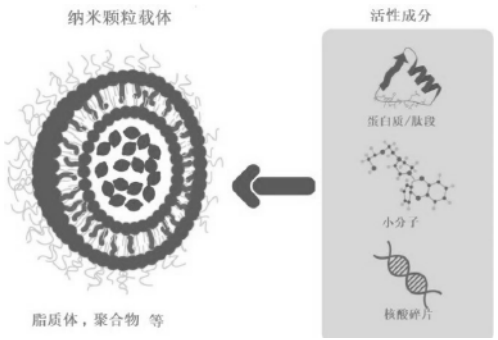
非共价组装

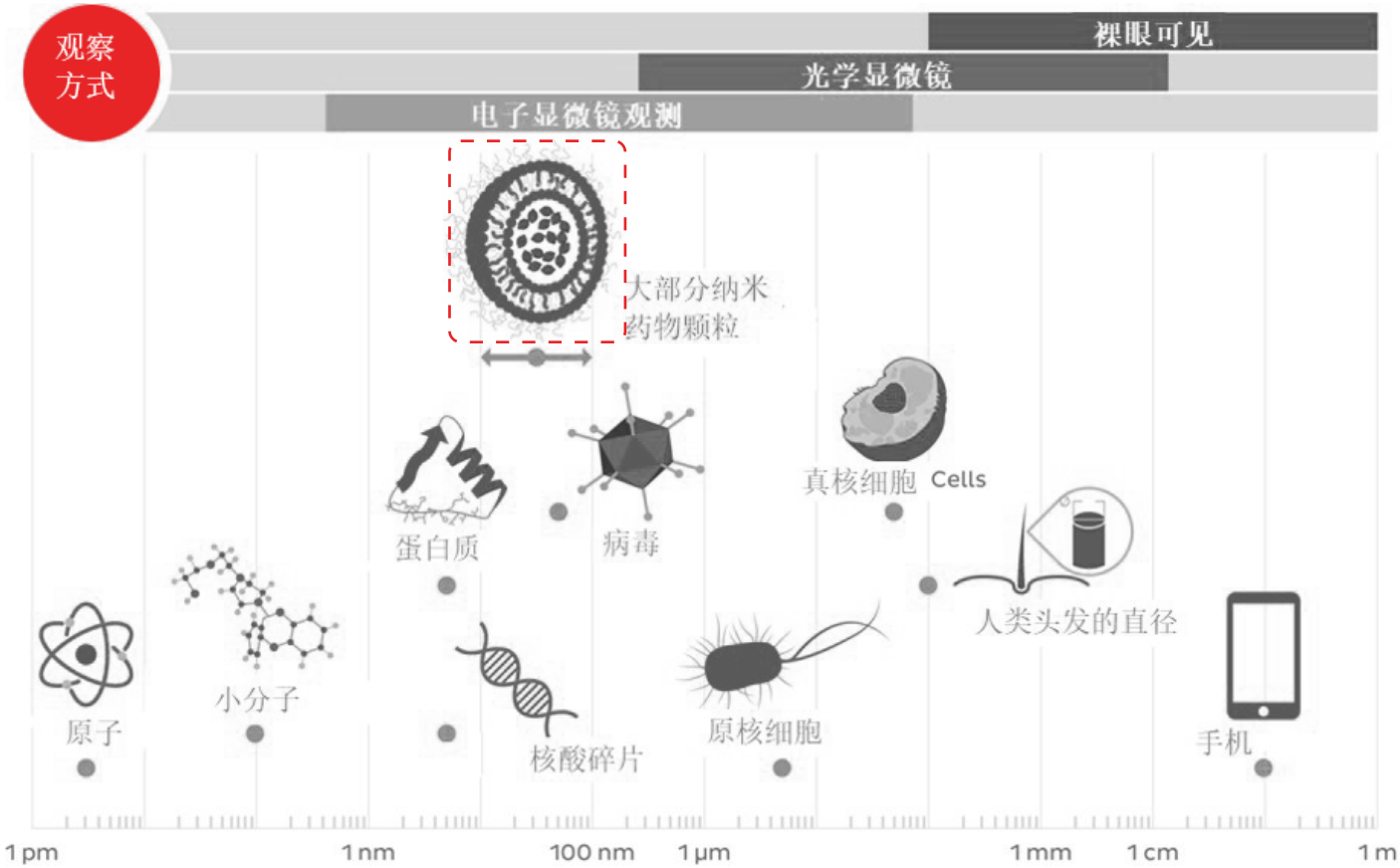


多重组装

纳米药物

1、纳米尺寸





2、纳米药物

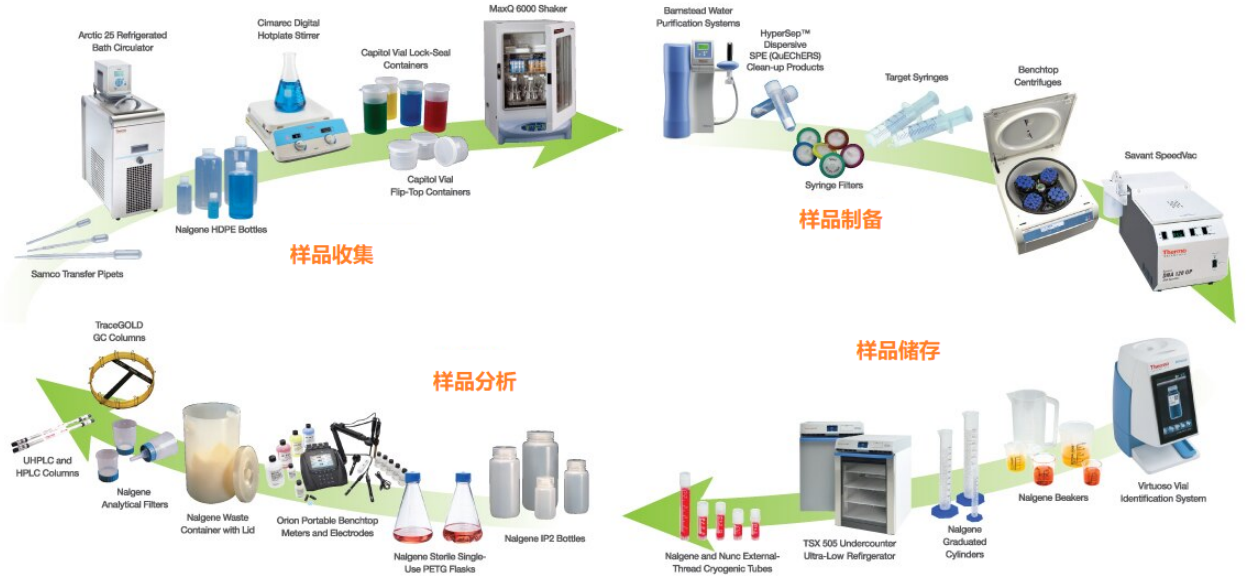
- 采用纳米载体物理包载或化学偶联药物的纳米药物制剂
- 自身具有药理活性的纳米材料

纳米药物主要研究工具

纳米药物合成与制备	药物材料表征	细胞水平评价	动物水平评价
• 药物与递送系统结合 • 药物浓缩 • 均一药物获得	• 药物形貌 • 粒度与粒径分布 • 表面成分及价态检测 • 结构检测与验证	• 细胞培养与储存 • 给药前后细胞形态观察 • 给药前后细胞功能检测	• 动物样品的制备与储存 • 动物病理模型 • 生物样本分析

化学键合法
物理包埋法

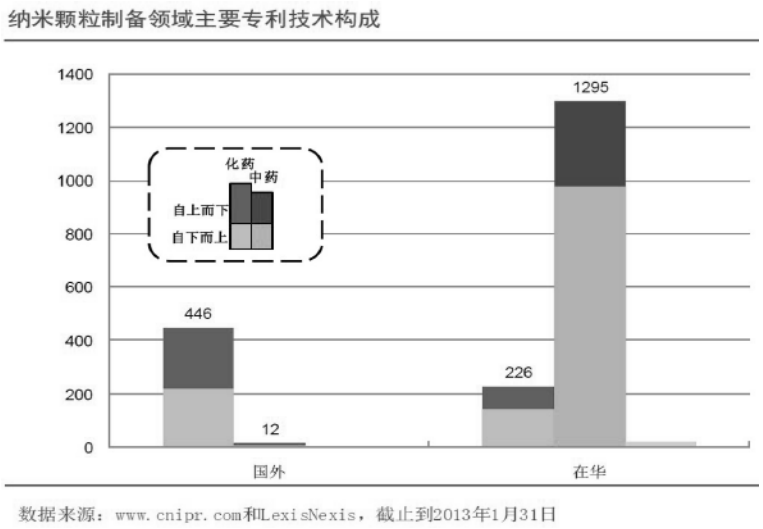
纳米药物的表面理化性质、尺寸、表面电荷及形貌等



纳米药物研究过程中的常见实验室设备与仪器

纳米药物合成与制备

- 加热磁力搅拌器
- 介质研磨机
- 真空干燥箱
- 冷冻干燥机
- 旋转蒸发仪
- 烘箱
- ……

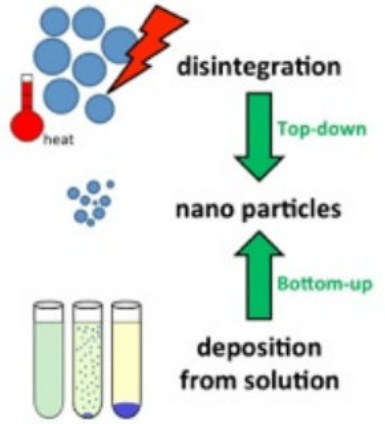


加热磁力搅拌器

注射纳米混悬剂的制备方法：

1、自上而下
- 介质研磨
- 高压均质

2、自下而上
- 沉淀法
- 乳化蒸发法
- 超临界法
- 冷冻干燥法



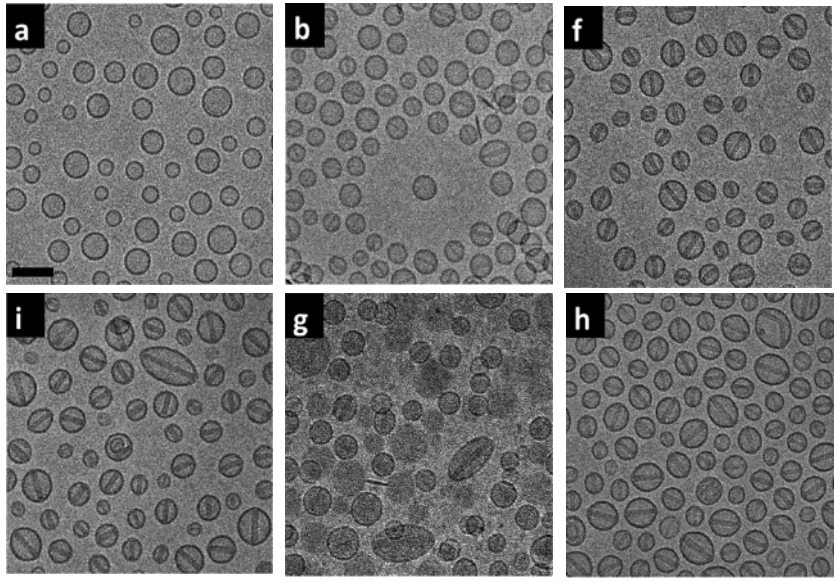
介质研磨机

纳米药物研究过程中的常见实验室设备与仪器

材料表征

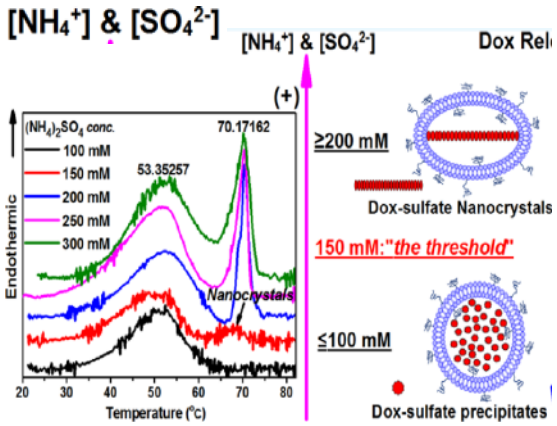
- 扫描探针显微技术
- 扫描电镜
- 透射电镜
- 粒度分析仪
- XPS
- XRD
- 表面与孔隙度分析仪
- 差式扫描量热仪
- 核磁共振
- ……

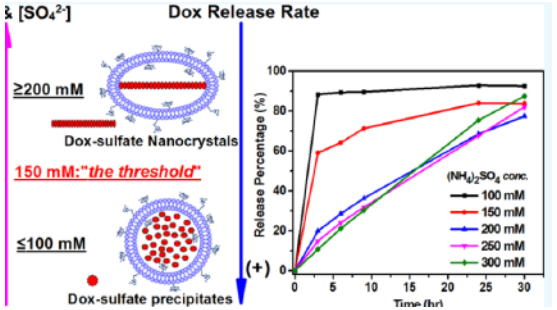
粒径（尺寸）/ 粒径分布、表面电荷、形状、结构、组成、纯度、稳定性、分散、表面特性



定量Cryo-TEM分析 不同硫酸铵制备的空白250 mM AS SUV和PLD

DOI: 10.1021/acsomega.7b01235
ACS Omega 2018, 3, 2508−2517

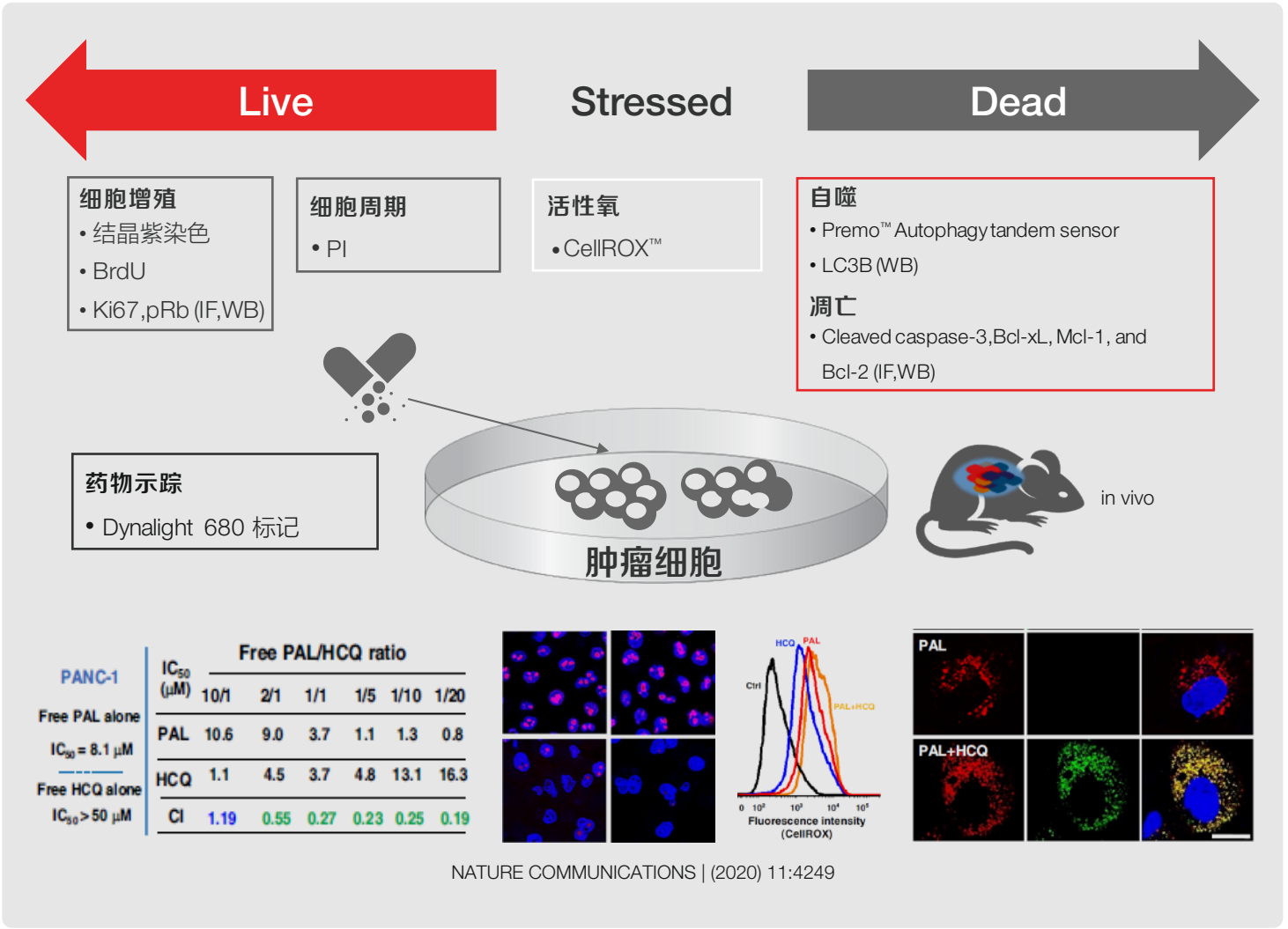




药物效力检测

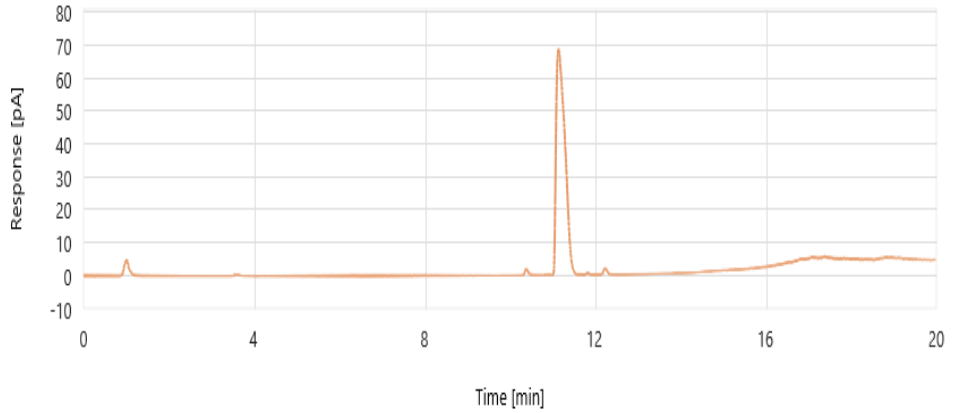
细胞水平评价

- 恒温CO_2细胞培养箱
- 生物安全柜
- 细胞培养基
- 倒置光学显微镜
- 激光共聚焦显微镜
- 流式细胞仪
- 细胞记数仪
- HPLC
- LCMSMS
- ……

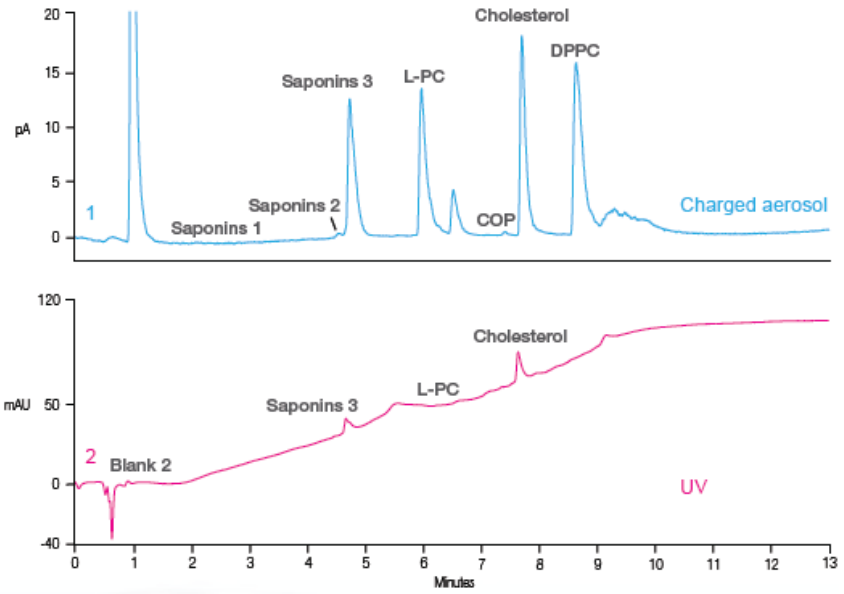


NATURE COMMUNICATIONS | (2020) 11:4249

CAD检测器用于脂质体等纳米药物研发



Purity of the Liposomal Biotherapeutic Delivery Compound, DDAB, by HPLC-CAD



Lipid-Based Formulations

Column:	Thermo Scientific™ **Hypersil GOLD™ PFP**	1.9 um, 2.1 × 100 mm
Mobile phase A:	0.1% Formic acid in water	
Mobile phase B:	0.1% Formic acid in 10:90 acetonitrile: reagent alcohol	
Gradient:	35% B to 83%B in 6 min to 90% B in 10 min	
Flow rate:	0.46 mL/min	
Inj. volume:	2 µL	
Col. temp:	45 °C	
Evap. temp:	**50 °C**	

纳米药物研究过程中的常见实验室设备与仪器

纳米药物合成与制备

加热磁力搅拌器

安全型烘箱

介质研磨机

真空加热干燥箱

冷冻干燥机

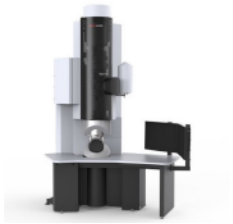
恒温水浴锅

材料表征

X射线光电子能谱仪（XPS）

X-射线衍射仪（XRD）

Quattro扫描电镜



Themis透射电镜

细胞水平评价

细胞培养

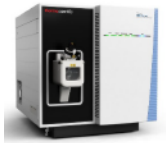
细胞分析

动物水平评价

超低温冰箱

冷冻切片机

Vanquish-UHPLC



液质三重四级杆

Orbitrap高分辨质谱

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